REMARKS / ARGUMENTS

The Claims

Claims 37-49 are currently pending in the application. Claim 42 has been amended to correct the antecedent basis and does not narrow or limit the scope thereof.

New claims 50-66 have been added. Claims 50 and 51 recite an antibody which binds a membrane associated or soluble osteoprotegerin binding protein (hereafter "OPGbp"). Support for these claims is found, for example, at p. 22, lines 20-25 of the specification. Claims 52-66 recite a method of inhibiting osteoclastogenesis by administering a modulator of OPGbp wherein the modulator is an antibody which binds OPGbp. Support for these claims are found, for example, at p. 18, lines 6-10 of the specification. No new matter has been introduced nor any new issues raised which would require further consideration and/or search. Entry of the amendment and new claims is respectfully requested.

Rejection under 35 U.S.C. 112

Claims 37-49 stand rejected under 35 U.S.C. 112, first paragraph, as the specification allegedly fails to enable the subject matter of the claims. The grounds for rejection presently set forth are nearly identical to those in the Office Action of February 24, 2000 (Paper No. 11).

The rejection should be withdrawn for the following reasons:

1) It fails to establish a *prima facie* case of nonenablement because there is no evidence or reasoning as to why the specification does not enable one to make and use the claimed subject matter; and

2) It fails to respond to or even acknowledge the arguments and evidence presented in the responses of August 18, 2000 and December 6, 1999, including evidence presented in a declaration.

In order to make a rejection for lack of enablement, the initial burden is on the Examiner to explain why the disclosure fails to enable the claimed invention and to back up such assertions with acceptable evidence or reasoning. *In re Marzochi* 169 USPQ2d at 370. No such evidence or reasoning has been presented.

The Examiner's position can be summarized on p. 4 of the present Office Action:

> The method instantly claimed is not enabled because contrary to applicants assertion the specification has not taught how to identify, predict or screen for those antibodies which not only bind to OPGbp, but modulate OPGbp activity such that bone resorption is inhibited.

Applicant maintains that Example 11, even though it is a prophetic example, teaches one how to identify and screen for anti-OPGbp antibodies. Example 11 describes various OPGbp peptides and polypeptides that may be used as immunogens, including peptides from the BB' loop and the EF loop regions of OPGbp which may be important for activity of OPGbp. Also taught in Example 11 are immunization protocols for raising antibodies in both mice and rabbits, enzyme linked immunosorbent assays (EIAs) for screening antibodies for binding to a selected OPGbp antigen, and cell fusion techniques for preparing hybridomas and monoclonal antibodies. Using the teachings in the specification of the BB' and EF loops of OPGbp, one skilled in the art would be able to generate antibodies which would inhibit OPGbp activity. Thus there is sufficient guidance in the specification for obtaining the claimed invention.

In addition to teaching how to obtain anti-OPGbp antibodies, the specification also teaches how to identify those antibodies which inhibit osteoclast formation and bone resorption. Example 8 describes an assay showing an increase in osteoclastogenesis by OPGbp. Example 9 describes an assay showing an increase in bone resorption by OPGbp. One skilled in the art could readily add an anti-OPGbp antibody to one or both of the assays in order to determine the effects of an antibody on either osteoclastogenesis and/or bone resorption. Moreover, the specification at p. 18, line 6 clearly contemplates adding antibodies to these assays in order to test their effects on OPGbp activity.

The Examiner has failed provide any reasoning as to why Examples 8, 9 and 11, and other relevant sections of the specification fail to enable the claimed methods. The only argument advanced by the Examiner is that there are no working examples of anti-OPGbp antibodies. However, there is no evidence that working examples of anti-OPGbp antibodies are required for enablement, especially given the extensive guidance and direction in the specification for making and using such antibodies combined with the knowledge of one skilled in the art in preparing antibodies.

It is also argued that the quantity of experimentation to identify antibodies which bind and inhibit bone resorption would result in undue experimentation. There is no indication whatsoever of what quantity of experimentation would be undue and no evidence presented which would suggest that the identification of anti-OPGbp antibodies which inhibit osteoclastogenesis or bone resorption would require any amount of experimentation that is undue. In making this allegation, the Examiner again ignores the teachings of the specification.

Even assuming for the sake of argument that a *prima facie* case of nonenablement could be established, the Examiner has failed to address any of the evidence in rebuttal presented by Applicant, in particular the evidence presented in the response of August 18, 2000.

Applicants reiterate the arguments and evidence presented on the record to date and specifically point out that evidence which has been presented in rebuttal and ignored by the Examiner:

The Examiner has ignored two references provided by the Applicant to rebut the Examiner's allegation that the art is unpredictable with respect to the generation of antagonist antibodies. The references are Yamamato et al. (Microbiol. Immunol. 32, 339-350 (1988)) and Siegel et al. (Cytokine 7, 15-25 (1995)) which described inhibitory antibodies to γ-interferon and tumor necrosis factor α (TNF-α), respectively. In both cases, the references showed that the mechanism for inhibition was the ability of antibodies to block binding of γ-interferon or TNF-α to its corresponding receptor.

The Examiner has ignored the relevant sections of the Federal Circuit's decision in *Wands* which clearly states that generating antibodies to a given immunogen and the testing of those antibodies is well within the level of skill in the art absent any evidence to the contrary. In the present case, there has been no evidence presented that generating anti-OPGbp antibodies and testing said antibodies for their ability to block OPGbp binding to its receptor and the ability to block osteoclast formation could not be carried out by one skilled in the art without undue experimentation.

The Examiner has ignored the Declaration of John K. Sullivan which showed that one skilled in the art could obtain anti-OPGbp antibodies which block osteoclast formation without undue

experimentation. The antibodies disclosed in the declaration were generated by using materials and methods substantially disclosed in the application. Yet, in the subsequent communication, the declaration was not even mentioned and the rejection was maintained on identical grounds. It is a clear error to dismiss a declaration of a person skilled in the art without adequate explanation of how the declaration failed to overcome the alleged *prima facie* case for rejection. *In re Alton* 37 USPQ2d 1578 (Fed. Cir. 1996)

In view of the remarks above, the rejection under 35 U.S.C. 112, first paragraph, should be withdrawn.

Rejection under 35 U.S.C. 102

Claims 37 and 38 are rejected under 35 U.S.C. 102(a) as being anticipated by Tsukii et al. (Biochem. Biophys. Res. Comm 246, 337-341 (1998) as evidenced by Takahashi et al. (cited in connection with the 112 rejection above). The Examiner notes the polyclonal antibody referenced in the abstract on p. 337, the text on p. 339, and Figures 2 and 3 of the Tsukii reference. Reconsideration is requested.

The rejection under 102(a) is incorrect. Section 102(a) states in part that a patent shall not be granted if the invention was patented or described in a printed publication "before the invention thereof by the applicant". The Tsukii reference cited under this section has a publication date of May 8, 1998 as evidenced by copies of the title page and table of contents attached hereto as Exhibit A. The present application has a filing date of June 23, 1997 and claims priority to U.S. Serial No. 08/842,842 filed on April 16, 1997. The Tsukii reference was published more than one full year after the Applicant's priority date and consequently cannot be prior art under 102(a). It is requested that the rejection be withdrawn.

CONCLUSION

Upon entry of the new claims, Claims 37-66 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

42. (amended) The [composition] method of Claim 38 [which comprises] wherein the antibody is a human antibody or fragment thereof.

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Exhibit A

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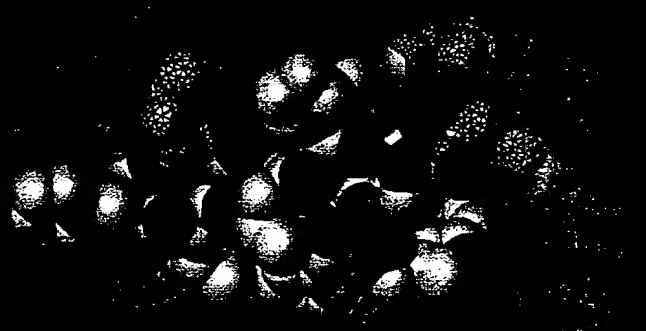

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